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     (FILE 'USPAT' ENTERED AT 09:54:08 ON 04 DEC 1997)
L1           156 S TGF(4N)BETA(4N)3
L2        151582 S WOUND?
L3         72514 S HEAL?
L4           753 S FGF
L5            13 S L1(P)L2(P)L3
L6           173 S L4(P)L3(P)L2
L7             1 S L6(P)L1

=> t l5 leg kwic 1-13


US PAT NO:      5,662,904 :IMAGE AVAILABLE:            L5: 1 of 13
DATE ISSUED:    Sep. 2, 1997
TITLE:          Anti-scarring compositions comprising growth factor
                  neutralizing antibodies
INVENTOR:       Mark William James Ferguson, Stockport, England
                David Michael Foreman, Chorlton, United Kingdom
                Mamta Shah, Withington, United Kingdom
ASSIGNEE:       The Victoria University of Manchester, Manchester, England
                  (foreign corp.)
APPL-NO:        08/122,508
DATE FILED:     Sep. 27, 1993
ART-UNIT:       186
PRIM-EXMR:      Toni R. Scheiner
ASST-EXMR:      Nancy A. Johnson
LEGAL-REP:      Wallenstein & Wagner, Ltd.

US PAT NO:      5,662,904 :IMAGE AVAILABLE:            L5: 1 of 13

ABSTRACT:

 A composition for use in the treatment of wounds to inhibit scar
tissue formation during healing, comprising an effective amount of an
activity-inhibiting growth factor neutralizing agent or agents specific
against all TGF-.beta., except for TGF-.beta..sub.3,
and PDGF, together with a pharmaceutically acceptable carrier. A method
of preparing the composition and a method of administering the
composition to a host suffering from tissue wounding is also
disclosed.

SUMMARY:

BSUM(5)

 In adult humans and other mammalian vertebrates, wound healing
in tissues such as skin is generally a reparative process, in contrast to
a regenerative process which appears to take place in healing of
fetal and embryonic tissue. The outcome of a wound repair process
appears no be influenced by a number of different factors, including both
intrinsic parameters, e.g. tissue oxygenation; and extrinsic parameters,
e.g. wound dressings. There is, however, considerable evidence
indicating that the overall process of healing and repair of
wound damaged tissue, including the necessary innercellular
communication, is regulated in a coordinated manner in adult humans and
other mammals by a number of specific soluble growth factors which are
released within the wound environment (especially by degranulating
platelets and incoming macrophages) and which, amongst other things,
appear to induce neovascularisation, leucocyte chemotaxis, fibroblast
proliferation, migration and deposition of collagen and other
extracellular matrix molecules within the wounds. Such growth factors
that have been identified and isolated are generally specialised soluble
proteins or polypeptides and include transforming growth factor alpha
(TGF-.alpha.), transforming growth factor beta (TGF-.beta.1,
TGF-.beta.2, TGF-.beta.3 etc), platelet derived
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growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factors I and II (IGFI and IGFII) and. . .

SUMMARY:

BSUM(9)

The TGF-.beta. growth factor family, for example, is believed to have a particularly important regulating role in **wound** repair, especially in adult animals, as a stimulant of macrophage infiltration, fibroblast migration, and extracellular matrix synthesis, especially collagen synthesis. . . extent, are believed to act in cooperation with one another in the complex overall regulatory process that is involved in **wound healing**. Indeed, PCT/US90/05566 discloses the general use of antibodies to TGF-.beta. to reduce fibrosis in a rat kidney nephrosis induced model. However, it is now found that not all TGF-.beta. growth factors are fibrotic and that supressing the activity of **TGF.beta.-3** in particular is counter-productive.

US PAT NO: 5,660,857 :IMAGE AVAILABLE: L5: 2 of 13
DATE ISSUED: Aug. 26, 1997
TITLE: Biopolymer composites
INVENTOR: Carla A. Haynes, Glasgow, United Kingdom
Wilson Harvey, Stirling, United Kingdom
Paul W. Watt, Stirling, United Kingdom
ASSIGNEE: Johnson & Johnson Medical Inc., Arlington, TX (U.S. corp.)
APPL-NO: 08/437,905
DATE FILED: May 10, 1995
ART-UNIT: 152
PRIM-EXMR: Carlos Azpuru
LEGAL-REP: Andrew C. Farmer

US PAT NO: 5,660,857 :IMAGE AVAILABLE: L5: 2 of 13

SUMMARY:

BSUM(34)

The composites of the invention are particularly useful as **wound** dressings or implants or as dressings specifically for the treatment of burns. The hydrophobic nature of the material (the degree of hydrophobicity is dependant on the content of the oleaginous phase) may be used to reduce moisture loss from **wounds**, to reduce trauma on removal, or to deliver active agents to the **wound** site. In these **wound** dressings or implants, factors which may promote **wound healing** can be incorporated into the matrix, these include growth factors, glycosaminoglycans (GAGS) such as hyaluronic acid, chondroitin sulphate or the low molecular weight heparins. Furthermore additional factors which have potential to reduce **wound** scarring such as mannose-6-phosphate, **TGF-.beta.**.sub.**3**, and anti **TGF .beta.**.sub.1 and **.beta.**.sub.2 can be dissolved/suspended in either the hydrophobic or hydrophilic phases of these matrices.

US PAT NO: 5,656,587 :IMAGE AVAILABLE: L5: 3 of 13
DATE ISSUED: Aug. 12, 1997
TITLE: Promotion of cell proliferation by use of transforming growth factor beta (TGF-.beta.)
INVENTOR: Michael B. Sporn, Bethesda, MD
Anita B. Roberts, Bethesda, MD
ASSIGNEE: The United States of America as represented by the Secretary of the Department of Health and Human Services , Washington, DC (U.S. corp.)
APPL-NO: 08/048,956

DATE FILED: Apr. 16, 1993
ART-UNIT: 181
PRIM-EXMR: Vasu S. Jagannathan
ASST-EXMR: Christine Saoud
LEGAL-REP: Birch, Stewart, Kolasch & Birch, LLP

US PAT NO: 5,656,587 :IMAGE AVAILABLE: L5: 3 of 13

DETDESC:

DETD(23)

TABLE 2

Wound healing response to bovine salivary gland or kidney TGF after 5
days of treatment.
TGF-.beta.s were prepared and injected as described.. . . .mu.g in Expt. 3, and 0.7 .mu.g in Expt. 2. All doses of
EGF were 20 ng. Total protein
in **wound** chambers was measured by the method of Lowry et al.
Statistical analysis of the data
was made by comparison of. . . P-30) + EGF
2 TGF-.beta. (Salivary
BSA 9 8.4 2.9 4.6 .+-. 1.0
<0.02
HPLC) + EGF
3 TGF-.beta. **(Kidney**
BSA 9 8.1 3.5 5.2 .+-. 1.5
<0.005
P-30) + EGF
4 TGF-.beta. (Salivary
EGF. . .

US PAT NO: 5,635,489 :IMAGE AVAILABLE: L5: 4 of 13
DATE ISSUED: Jun. 3, 1997
TITLE: Methods of prevention of oral mucositis with transforming growth factor .beta.
INVENTOR: John D. Haley, Great Neck, NY
ASSIGNEE: Oncogene Science, Inc., Uniondale, NY (U.S. corp.)
APPL-NO: 08/395,909
DATE FILED: Feb. 28, 1995
ART-UNIT: 181
PRIM-EXMR: Jill Warden
ASST-EXMR: P. Lynn Touzeau
LEGAL-REP: John P. White

US PAT NO: 5,635,489 :IMAGE AVAILABLE: L5: 4 of 13

DETDESC:

DETD(29)
These data were statistically significant and conclusively show TGF-.beta.3 **reduces the severity and duration of mucositis in vivo (FIGS. 2-5). Increased survival (FIG. 6) and weight retention (FIG. 7). . . This effect was achieved through cell cycle inhibition of the oral epithelium prior to chemotherapy, and not apparently by accelerated** wound healing, **as shown by Example 5.**

US PAT NO: 5,599,788 :IMAGE AVAILABLE: L5: 5 of 13
DATE ISSUED: Feb. 4, 1997
TITLE: Method for accelerating skin wound healing with H3 protein

INVENTOR: Anthony F. Purchio, Cardiff, CA
Richard LeBaron, Temecula, CA
ASSIGNEE: Advanced Tissue Sciences, La Jolla, CA (U.S. corp.)
APPL-NO: 08/268,797
DATE FILED: Jul. 1, 1994
ART-UNIT: 182
PRIM-EXMR: John Ulm
ASST-EXMR: Prema Mertz
LEGAL-REP: Knobbe, Martens, Olson & Bear

US PAT NO: 5,599,788 :IMAGE AVAILABLE: L5: 5 of 13

SUMMARY:

BSUM(5)

TGF-.beta. encompasses a family of dimeric proteins including TGF-.beta.1, TGF-.beta.2, TGF-.beta.3, TGF-.beta.4, and TGF-.beta.5 which regulate the growth and differentiation of many cell types (Barnard et al., (1990) Biochim. Biophys. Acta., 1032:79-87). Other members. . . adhesion, TGF-.beta. increases the expression of collagen and fibronectin (Ignotz et al., (1986) J. Biol. Chem., 261:4337-4345) and accelerates the **healing** of incisional wounds (Mustoe et al., (1987) Science, 237:1333-1335).

US PAT NO: 5,591,716 :IMAGE AVAILABLE: L5: 6 of 13
DATE ISSUED: Jan. 7, 1997
TITLE: Beneficial wound healing applications of calreticulin and other hyaluronan-associated proteins
INVENTOR: John W. Siebert, New York, NY
Hari G. Garg, Belmont, MA
Leslie I. Gold, New York, NY
ASSIGNEE: New York University, New York, NY (U.S. corp.)
The General Hospital Corp., Boston, MA (U.S. corp.)
APPL-NO: 08/155,933
DATE FILED: Nov. 19, 1993
ART-UNIT: 188
PRIM-EXMR: Chhaya D. Sayala
LEGAL-REP: Morrison & Foerster LLP

US PAT NO: 5,591,716 :IMAGE AVAILABLE: L5: 6 of 13

SUMMARY:

BSUM(38)

Also provided is a method for modulating the expression of TGF.beta. isoforms in the healing tissue of a wound in a subject, such that TGF.beta.3 expression is enhanced and TGF.beta.1 expression and TGF.beta.2 expression are inhibited, which method comprises administering to the subject an amount of a hyaluronan-associated protein, or a functional derivative thereof, effective in enhancing TGF.beta.3 and inhibiting TGF.beta.1 and TGF.beta.2.

DETDESC:

DETD(28)

In . . . A functional derivative retains at least a portion of the function of calreticulin, such as the activity of promoting scarless wound healing, upregulating TGF.beta.3 expression in skin, or binding to a specific anti-calreticulin antibody, which permits its utility in accordance with the present invention.

US PAT NO: 5,550,151 :IMAGE AVAILABLE: L5: 7 of 13
DATE ISSUED: Aug. 27, 1996
TITLE: Methods of reducing scarring in wound healing
INVENTOR: George J. Cullinan, Trafalgar, IN
ASSIGNEE: Eli Lilly Company, Indianapolis, IN (U.S. corp.)
APPL-NO: 08/293,851
DATE FILED: Aug. 22, 1994
ART-UNIT: 125
PRIM-EXMR: Russell Travers
LEGAL-REP: James J. Sales, David E. Boone

US PAT NO: 5,550,151 :IMAGE AVAILABLE: L5: 7 of 13

SUMMARY:

BSUM(7)

TGF-.beta. . . . of the family either share amino acid homology and/or have similar physiological actions. Of particular interest to the subject of wound healing are: **TGF**-.**beta**.s 1, 2, and 3. For further discussion of the TGF-.beta. family of peptides, the subject is reviewed in Roberts A. B. and Sporn M.. . . Factor-.beta.s.", Sporn and Roberts, eds; "Peptide Growth Factors and Their Receptors I". Berlin, Springer Verlag, 1990 419-472. Additionally, TGF-.beta.s in wound healing, references in Ferguson, ibid., are germane.

SUMMARY:

BSUM(8)

Very . . . in experimental, animal scar models that TGF-.beta.1 appears to exacerbate the formation of scar tissue. However, it was shown that TGF-.beta.3 protected the skin from scar formation and allowed normal healing of the wound. The proposed mechanism for this action of TGF-.beta.3 was the decrease in macrophage and monocyte infiltration at the wound site. Ferguson, M. W., "Wound Healing, Scarring, TGF-.beta. antagonists and Isoforms," Abst. NIH TGF-.beta. Symposia, Bethesda Md., May 3, 1994.

US PAT NO: 5,496,828 :IMAGE AVAILABLE: L5: 8 of 13
DATE ISSUED: Mar. 5, 1996
TITLE: Methods of inhibiting ulcerative mucositis
INVENTOR: George J. Cullinan, Trafalgar, IN
ASSIGNEE: Eli Lilly and Company, Indianapolis, IN (U.S. corp.)
APPL-NO: 08/293,790
DATE FILED: Aug. 22, 1994
ART-UNIT: 125
PRIM-EXMR: Jerome D. Goldberg
LEGAL-REP: James J. Sales

US PAT NO: 5,496,828 :IMAGE AVAILABLE: L5: 8 of 13

SUMMARY:

BSUM(8)

TGF-.beta. . . . of the family either share amino acid homology and/or have similar physiological actions. Of particular interest to the subject of wound healing are: **TGF**-.**beta**.s 1, 2, and 3. For further discussion of the TGF-.beta. family of peptides, the subject is reviewed in: Roberts et al., The transforming growth. . .

US PAT NO: 5,449,671 :IMAGE AVAILABLE: L5: 9 of 13
DATE ISSUED: Sep. 12, 1995
TITLE: Use of TGF-.beta.3, to prevent or retard fistula closure following glaucoma filtration surgery
INVENTOR: Jon C. Nixon, Fort Worth, TX
Billie M. York, Fort Worth, TX
ASSIGNEE: Alcon Laboratories, Inc., Fort Worth, TX (U.S. corp.)
APPL-NO: 08/129,962
DATE FILED: Sep. 29, 1993
ART-UNIT: 181
PRIM-EXMR: Jill Warden
ASST-EXMR: Plynn Touzeau
LEGAL-REP: James A. Arno, Gregg C. Brown

US PAT NO: 5,449,671 :IMAGE AVAILABLE: L5: 9 of 13

SUMMARY:

BSUM(14)

The . . . thereby reduce the incidence of fistula closure. The method of the present invention utilizes a specific growth factor, transforming growth factor-beta-3 ("TGF-.beta..sub.3 "), as a mediator of the normal wound healing process.

SUMMARY:

BSUM(16)

In studies on fetal wounds, it has been noted that healing occurs rapidly without the scarring associated with the healing of adult wounds. Fetal wounds are thought to have relatively high levels of TGF-.beta..sub.3. TGF-.beta..sub.1 and basic fibroblast growth factor are present in neonatal and adult wounds, but are not detected in fetal wounds. See Whitby, et at., Devl. Biol., volume 147, pages 207-215 (1991). If fetal wounds are injected with TGF-.beta..sub.1, scarring will occur, and if a specific antibody to TGF-.beta..sub.1 is added to the wound, neutralizing the effects of the growth factor, scarfing will be prevented. See Shah, et at., Lancet, volume 339, pages 213-214. . .

SUMMARY:

BSUM(19)

In . . . the foregoing, it is clear that there are distinct differences between the in vivo activities of the .beta..sub.1, .beta..sub.2, and .beta..sub.3 isoforms of TGF-.beta.. This is particularly true with respect to TGF-.beta..sub.3. The present invention is based on a new application of the unique properties of TGF-.beta..sub.3. More specifically, the present invention utilizes the properties of TGF-.beta..sub.3 to alter the healing of wounds associated with glaucoma filtration surgery, so as to reduce the incidence of fistula closure by scar tissue.

US PAT NO: 5,422,340 :IMAGE AVAILABLE: L5: 10 of 13
DATE ISSUED: Jun. 6, 1995
TITLE: TGF-.beta.formulation for inducing bone growth
INVENTOR: Arthur J. Ammann, 460 Point San Bruno Blvd., South San Francisco, CA 94080-4990
Steven L. Beck, 460 Point San Bruno Blvd., South San

Francisco, CA 94080-4990
Tue H. Nguyen, 460 Point San Bruno Blvd., South San Francisco, CA 94080-4990
Boonsri Ongpipattanakul, 460 Point San Bruno Blvd., South San Francisco, CA 94080-4990
Christopher G. Rudman, 460 Point San Bruno Blvd., South San Francisco, CA 94080-4990
APPL-NO: 08/255,844
DATE FILED: Jun. 8, 1994
ART-UNIT: 181
PRIM-EXMR: Howard E. Schain
ASST-EXMR: P. Lynn Touzeau

US PAT NO: 5,422,340 :IMAGE AVAILABLE: L5: 10 of 13

DETDESC:

DETD(110)

In . . . as a mixture of immature and mature bone. This indicates active formation and resorption processes that are natural to bone healing. Remodeling of bone was confirmed histomorphometrically by an increase in both bone formation and resorption parameters within TGF-.beta.1-treated sites. The results indicate that the defect area is much lower after application of the TCP granules with 25 .mu.g/ml (3 .mu.g/wound site) TGF-.beta. and is even still lower after application of the TCP granules with 100 .mu.g/ml (14 .mu.g/wound site) TGF-.beta.. TCP granules without TGF-.beta.1 were minimally inductive at 28 days with only slight amounts of bone located at. . .

US PAT NO: 5,411,940 :IMAGE AVAILABLE: L5: 11 of 13
DATE ISSUED: May 2, 1995
TITLE: Use of TGF-.beta..sub.3 to reduce the formation of scar tissue in response to corneal trauma
INVENTOR: Jon C. Nixon, Fort Worth, TX
Billie M. York, Fort Worth, TX
ASSIGNEE: Alcon Laboratories, Inc., Fort Worth, TX (U.S. corp.)
APPL-NO: 08/128,460
DATE FILED: Sep. 29, 1993
ART-UNIT: 181
PRIM-EXMR: Howard E. Schain
ASST-EXMR: P. Lynn Touzeau
LEGAL-REP: James A. Arno, Gregg C. Brown

US PAT NO: 5,411,940 :IMAGE AVAILABLE: L5: 11 of 13

SUMMARY:

BSUM(6)

In studies on fetal wounds, it has been noted that healing occurs rapidly without the scarring associated with the healing of adult wounds. Fetal wounds are thought to have relatively high levels of TGF-.beta..sub.3. TGF-.beta..sub.1 and basic fibroblast growth factor are present in neonatal and adult wounds, but are not detected in fetal wounds. See Whitby, et al., Devl. Biol., volume 147, pages 207-215 (1991). If fetal wounds are injected with TGF-.beta..sub.1, scarring will occur, and if a specific antibody to TGF-.beta..sub.1 is added to the wound, neutralizing the effects of the growth factor, scarring will be prevented. See Shah, et at., Lancet, volume 339, pages 213-214. . .

SUMMARY:

BSUM(9)

In . . . the foregoing, it is clear that there are distinct differences between the in vivo activities of the .beta..sub.1, .beta..sub.2, and .beta..sub.3 isoforms of TGF-.beta.. This is particularly true with respect to TGF-.beta..sub.3. The present invention is based on a new application of the unique properties of TGF-.beta..sub.3. More specifically, the present invention utilizes the properties of TGF-.beta..sub.3 to alter the healing of corneal wounds, so as to prevent scar formation.

SUMMARY:

BSUM(12)

The improved method of the present invention utilizes a specific growth factor, transforming growth factor-beta-3 ("TGF-.beta..sub.3 "), as a mediator of the normal wound healing process. The properties of TGF-.beta..sub.3 are unique relative to the other known isoforms of TGF-.beta.. For example, TGF-.beta..sub.1 is known to up-regulate (i.e., stimulate) the secretion of extracellular matrix components by fibroblasts. In contrast, the specific response of stromal fibroblasts to TGF-.beta..sub.3 is believed to be a suppression of the inflammatory response, which may result in a relatively low production of extracellular. . .

SUMMARY:

BSUM(13)

While applicants do not wish to be bound by any theory, it is believed that TGF-.beta..sub.3 prevents or retards the formation of scar tissue at the site of the corneal trauma by altering the production and. . . alteration of the extracellular matrix components, particularly fibronectin, collagen and glycosaminoglycans, greatly reduces scarring normally associated with these components during wound healing. TGF-.beta..sub.3 is also believed to accelerate resurfacing of the corneal epithelium following trauma to the cornea by stimulating stromal cells to. . .

US PAT NO: 5,262,319 :IMAGE AVAILABLE: L5: 12 of 13
DATE ISSUED: Nov. 16, 1993
TITLE: Method for obtaining bone marrow free of tumor cells using transforming growth factor .beta.3
INVENTOR: Kenneth K. Iwata, Westbury, NY
J. Gordon Foulkes, Huntington, NY
Peter T. Dijke, Port Washington, NY
John D. Haley, Great Neck, NY
ASSIGNEE: Oncogene Science, Inc., Uniondale, NY (U.S. corp.)
APPL-NO: 07/543,341
DATE FILED: Jun. 25, 1990
ART-UNIT: 186
PRIM-EXMR: David L. Lacey
ASST-EXMR: Robert D. Budens
LEGAL-REP: John P. White

US PAT NO: 5,262,319 :IMAGE AVAILABLE: L5: 12 of 13

DETDESC:

DETD(125)

In the presence of EGF, acidified conditioned media from CHO 6.35,

containing TGF-.beta.3 was able to promote soft agar growth of NRK cells. Growth of NRK cells in soft agar has been shown to be inducible by stimulating the production of extracellular matrix proteins, an important parameter in wound healing.

DETDESC:

DETD(239)

TGF-.beta.3 enhances cell growth, alone or in combination with other molecules. For example, TGF-.beta.3 may directly affect DNA synthesis. Alternatively, TGF-.beta.3 synergizes with other factors to promote cell growth. Accordingly, when contacted with fibroblasts in vitro or in vivo, TGF-.beta.3 acts to promote connective tissue repair, dermatological repair and wound healing.

US PAT NO: 5,104,977 :IMAGE AVAILABLE: L5: 13 of 13
DATE ISSUED: Apr. 14, 1992
TITLE: Purified transforming growth factor beta
INVENTOR: Michael B. Sporn, Bethesda, MD
Anita B. Roberts, Bethesda, MD
Richard K. Assoian, Dobbs Ferry, NY
Charles A. Frolik, Indianapolis, IN
ASSIGNEE: The United States of America as represented by the Department of Health and Human Services, Washington, DC (U.S. govt.)
APPL-NO: 07/308,948
DATE FILED: Feb. 8, 1989
ART-UNIT: 186
PRIM-EXMR: Garnette D. Draper
LEGAL-REP: Birch, Stewart, Kolasch & Birch

US PAT NO: 5,104,977 :IMAGE AVAILABLE: L5: 13 of 13

DETDESC:

DETD(17)

TABLE 2

Wound healing response to bovine salivary gland or kidney TGF after 5
days of treatment.
TGF-.beta.s were prepared and injected as described.. . . .mu.g in Expt. 3, and 0.7 .mu.g in Expt. 2. All
doses of EGF were 20 ng.
Total protein in wound chambers was measured by the method of Lowry et
al. Statistical analysis
of the data was made by comparison of. . . P-30) + EGF
2 TGF-.beta. (Salivary
BSA 9 8.4 2.9 4.6 .+-. 1.0
<0.02
HPLC) + EGF
3 TGF-.beta. (Kidney
BSA 9 8.1 3.5 5.2 .+-. 1.5
<0.005
P-30) + EGF
4 TGF-.beta. (Salivary
EGF. . .

=> t l6 leg kwic 160-173

US PAT NO: 5,023,090 :IMAGE AVAILABLE: L6: 160 of 173
DATE ISSUED: Jun. 11, 1991
TITLE: Topical compositions containing LYCD and other topically active medicinal ingredients for the treatment of ACNE
INVENTOR: Robert H. Levin, 11127 Jardin Pl., Cincinnati, OH 45241
APPL-NO: 07/503,225
DATE FILED: Apr. 2, 1990
ART-UNIT: 188
PRIM-EXMR: Douglas W. Robinson
ASST-EXMR: Jean Witz
LEGAL-REP: Samuel Kurlandsky

US PAT NO: 5,023,090 :IMAGE AVAILABLE: L6: 160 of 173

DETDESC:

DETD(64)

Epidermal . . . Factor (EGF) is one such growth factor which has been used topically at a concentration of 0.0001% to accelerate normal **wound healing** by 15-20 percent. According to the method of the present invention, compositions containing 500 units of LYCD as SRF (approximately. . . at 0.1% to 0.5% concentrations (equivalent to 200-1000 LYCD units per ounce of product) in compositions with Fibroblast Growth Factor (**FGF**), Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-alpha (TGF-alpha), Transforming Growth Factor-beta (TGF-beta), or Insulin-like Growth Factor-1 (IGF-1) has provided synergistic **wound healing** compositions. Both partial and full incisional **wounds** show synergistic **healing** patterns. Compositions consisting of several of these growth factors formulated with LYCD as in LYCODERM.RTM. also result in synergistically acting **wound healing** products.

US PAT NO: 5,019,559 :IMAGE AVAILABLE: L6: 161 of 173
DATE ISSUED: May 28, 1991
TITLE: Wound healing using PDGF and IGF-II
INVENTOR: Harry N. Antoniades, Newton, MA
Samuel E. Lynch, Jamaica Plain, MA
ASSIGNEE: President and Fellows of Harvard College, Cambridge, MA (U.S. corp.)
APPL-NO: 07/272,090
DATE FILED: Nov. 16, 1988
ART-UNIT: 186
PRIM-EXMR: Howard E. Schain

US PAT NO: 5,019,559 :IMAGE AVAILABLE: L6: 161 of 173

SUMMARY:

BSUM(4)

It has been proposed to use PDGF to promote in vivo **wound healing**. For example, Grotendorst (1984) J. Trauma 24:549-52 describes adding PDGF to Hunt-Schilling wire mesh chambers impregnated with a collagen gel. . . amount of new collagen synthesized. However, Leitzel et al. (1985) J. Dermatol. Surg. Oncol. 11:617-22 were unable to accelerate normal **wound healing** in hamsters using PDGF alone or in combination with **FGF** and EGF.

US PAT NO: 5,013,649 :IMAGE AVAILABLE: L6: 162 of 173
DATE ISSUED: May 7, 1991

TITLE: DNA sequences encoding osteoinductive products
INVENTOR: Elizabeth A. Wang, Carlisle, MA
John M. Wozney, Hudson, MA
Vicki Rosen, Brookline, MA
ASSIGNEE: Genetics Institute, Inc., Cambridge, MA (U.S. corp.)
APPL-NO: 07/179,100
DATE FILED: Apr. 8, 1988
ART-UNIT: 185
PRIM-EXMR: Robin L. Teskin
ASST-EXMR: Joan Ellis
LEGAL-REP: Ellen J. Kapinos, Bruce M. Eisen

US PAT NO: 5,013,649 :IMAGE AVAILABLE: L6: 162 of 173

SUMMARY:

BSUM(7)

Another . . . effective amount of a BMP-2 protein in a pharmaceutically acceptable vehicle or carrier. BMP-2 compositions may also be used for **wound healing** and tissue repair. The invention further provides pharmaceutical compositions containing a therapeutically effective amount of BMP-2A or BMP-2B in a. . . and Ser. No. 179,197. Other therapeutically useful agents include growth factors such as epidermal growth factor (EGF), fibroblast growth factor (**FGF**), and transforming growth factor (TGF). The compositions may also include an appropriate matrix for instance, for supporting the composition and. . . may be employed in methods for treating a number of bone and/or cartilage defects, periodontal disease and various types of **wounds**. These methods, according to the invention, entail administering to a patient needing such bone and/or cartilage formation **wound healing** or tissue repair, an effective amount of a BMP-2 protein such as BMP-2A and/or BMP-2B. These methods may also entail. . .

US PAT NO: 4,950,483 :IMAGE AVAILABLE: L6: 163 of 173
DATE ISSUED: Aug. 21, 1990
TITLE: Collagen wound healing matrices and process for their production
INVENTOR: George Ksander, Redwood City, CA
Yasushi Ogawa, Pacifica, CA
ASSIGNEE: Collagen Corporation, Palo Alto, CA (U.S. corp.)
APPL-NO: 07/286,303
DATE FILED: Dec. 16, 1988
ART-UNIT: 158
PRIM-EXMR: Thurman Page
LEGAL-REP: Irella & Manella

US PAT NO: 4,950,483 :IMAGE AVAILABLE: L6: 163 of 173

ABSTRACT:
Collagen implants that are useful as **wound healing** matrices are characterized by being formed of collagen fibrils that are not chemically cross-linked, and having a bulk density of. . . size of 35 to 250 microns. The implants are capable of promoting connective tissue deposition, angiogenesis, reepithelialization, and fibroplasia. The **wound healing** matrix also serves an an effective sustained delivery system for synergistic combinations of **FGF** and TGF-B.

DETDESC:

DETD(18)

The addition of bioactive agents or protein factors enhances the ability of the **wound healing** matrices to promote **wound healing**.

The incorporation of approximately equal amounts of **FGF** and TGF-B significantly enhances granulation tissue deposition, angiogenesis, reepithelialization, and fibroplasia. The bioactive additives or protein factors used herein may. . . term "bioactive agent,""bioactive substance," and "bioactive additive," as well as within the specific terms used to denote particular factors, e.g., "**FGF**" and "TGF-beta." Such analogues may be made by conventional genetic engineering techniques, such as via expression of synthetic genes or. . .

CLAIMS:

CLMS(1)

What . . .
matrix comprises
fibrillar atelopeptide collagen, wherein said fibrils are about 50-200 nm in diameter, and are not chemically cross-linked; and
a synergistic **wound-healing** effective amount of TGF-B and **FGF**.

CLAIMS:

CLMS(3)

3. The sponge composition of claim 1 wherein said synergistic **wound-healing** effective amount of TGF-B and **FGF** is about 0.07 to about 200 ug per cm.sup.2 of composition.

CLAIMS:

CLMS(6)

6. A method for promoting **wound healing** in a mammal having a **wound**, which method comprises:
applying to said **wound** a collagen sponge composition having a density of about 0.01 to about 0.3 g/cm.sup.3, a thickness of about 1-20 mm,. . . matrix comprises
fibrillar atelopeptide collagen, wherein said fibrils are about 50-200 nm in diameter, and are not chemically cross-linked; and
a synergistic **wound-healing** effective amount of TGF-B and **FGF**.

CLAIMS:

CLMS(8)

8. The method of claim 6 wherein said synergistic **wound-healing** effective amount of TGF-B and **FGF** is about 0.07 to about 200 ug per cm.sup.2 of composition.

US PAT NO: 4,942,031 :IMAGE AVAILABLE: L6: 164 of 173
DATE ISSUED: Jul. 17, 1990
TITLE: Compositions containing LYCD and other topically active medicinal ingredients
INVENTOR: Robert H. Levin, 11127 Jardin Pl., Cincinnati, OH 45241
APPL-NO: 07/394,862
DATE FILED: Aug. 16, 1989
ART-UNIT: 188
PRIM-EXMR: Jacqueline Stone
ASST-EXMR: J. Witz
LEGAL-REP: Samuel Kurlandsky

US PAT NO: 4,942,031 :IMAGE AVAILABLE: L6: 164 of 173

DETDESC:

DETD(111)

Epidermal . . . Factor (EGF) is one such growth factor which has been used topically at a concentration of 0.0001% to accelerate normal **wound healing** by 15-20 percent. According to the method of the present invention, compositions containing 500 units of LYCD as TRF (approximately. . . at 0.1% to 0.5% concentrations (equivalent to 200-1000 LYCD/TRF units per ounce of product) in compositions with Fibroblast Growth Factor (**FGF**), Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-alpha (TGF-alpha), Transforming Growth Factor-beta (TGF-beta), or Insulin-like Growth Factor-1 (IGF-f) has provided synergistic **wound healing** compositions. Both partial and full incisional **wounds** show synergistic **healing** patterns. Compositions consisting of several of these growth factors formulated with LYCD/TRF as in LYCODERM.RTM. also result in synergistically acting **wound healing** products.

US PAT NO: 4,939,135 :IMAGE AVAILABLE: L6: 165 of 173
DATE ISSUED: Jul. 3, 1990
TITLE: Pharmaceutical compositions and methods of treatment to prevent and treat corneal scar formation produced by laser irradiation
INVENTOR: Stella M. Robertson, Arlington, TX
Herman M. Kunkle, Jr., Mansfield, TX
Michael E. Stern, Grapevine, TX
ASSIGNEE: Alcon Laboratories, Inc., Fort Worth, TX (U.S. corp.)
APPL-NO: 07/253,009
DATE FILED: Oct. 3, 1988
ART-UNIT: 125
PRIM-EXMR: Douglas W. Robinson
ASST-EXMR: Zohreh A. Fay
LEGAL-REP: James Arno, Sally Yeager

US PAT NO: 4,939,135 :IMAGE AVAILABLE: L6: 165 of 173

DETDESC:

DETD(15)

To prevent or reduce scar formation due to improper epithelial cell coverage of the cornea after photoablation, various **wound healing** modulators can be used. Prior to, or during, photoablation of the anterior surface of the cornea the epithelial cells are. . . re-epithelialization to occur. Improper epithelial cell coverage leading to scar formation may be prevented or alleviated through the use of **wound healing** modulators including growth factors such as EGF, IGF, PDGF, **FGF**, TGF.sub.B, TGF.sub.A and NGF and basement membrane components. These **wound healing** modulators can be used at concentrations previously discussed.

DETDESC:

DETD(17)

Concerning corneal haze formation resulting from scar formation attributable to inflammation, the following **wound healing** modulators can be used in accordance with the foregoing discussion: steroids; growth factors such as EGF, **FGF**, IGF, PDGF, TGF.sub.A, TGF.sub.B and NGF, and aldose reductase inhibitors. Additionally, nonsteroidal antiinflammatory agents (NSAIs) can be used as **wound healing** modulators to prevent or control corneal haze resulting from UV photoablation. Nonsteroidal antiinflammatory agents which can be used

according to. . .

DETDESC:

DETD(22)

Wound healing modulators which can be used to prevent or alleviate corneal haze resulting from improperly activated fibroblasts include: growth factors, such as EGF, **FGF**, TGF.sub.A, TGF.sub.B, NGF, PDGF, insulin like growth factor (IGF) and insulin; and tumor necrosis factor (TNF). Such growth factors can be used in accordance with the foregoing discussion of this class of **wound healing** modulators. In addition, the immunomodulators, antiallergics and basement membrane components, as previously set forth, can be used in this situation.

DETDESC:

DETD(24)

Wound healing modulators which can be used to prevent or alleviate the formation of corneal haze due to damage to collagen fibrils include: the growth factors TNF, EGF, **FGF**, IGF and insulin; steroids; immunomodulators, basement membrane components and antioxidants, all of which may be used as previously discussed.

DETDESC:

DETD(26)

Wound healing modulators which can be used to combat corneal haze resulting from dead or damaged fibroblasts include the growth factors EGF, **FGF**, PDGF, TGF.sub.A, TGF.sub.B and NGF, all of which may be used as previously discussed. In addition, fatty acid derivatives, which. . . clearance of the corneal haze. For a discussion regarding the regulation of macrophage-derived fibroblast growth factor, which is involved in **wound healing** and scar formation, by arachidonate metabolites, see Journal of Leukocyte Biology 42:106-113(1987), the contents of which are incorporated herein by. . .

DETDESC:

DETD(27)

A fifth possible cause of the corneal haze is the corneal edema which may occur following photoablation. **Wound healing** modulators which can be used to combat the formation of and treat corneal haze attributable to edema include: growth factors such as EGF, **FGF**, TGF.sub.A, TGF.sub.B and NGF; steroids; nonsteroidal antiinflammatories; antiallergics; anti-oxidants and aldose reductase inhibitors. Additionally antimicrobial compounds, discussed below, can be. . .

US PAT NO: 4,889,919 :IMAGE AVAILABLE: L6: 166 of 173
DATE ISSUED: Dec. 26, 1989
TITLE: Biologically active PDGF derived A-chain homodimers
INVENTOR: Mark J. Murray, Seattle, WA
James D. Kelly, Seattle, WA
ASSIGNEE: ZymoGenetics, Inc., Seattle, WA (U.S. corp.)
APPL-NO: 06/942,484
DATE FILED: Dec. 15, 1986
ART-UNIT: 186
PRIM-EXMR: Margaret Moskowitz
ASST-EXMR: Jeff P. Kushan
LEGAL-REP: Seed and Berry

US PAT NO: 4,889,919 :IMAGE AVAILABLE: L6: 166 of 173

DETDESC:

DETD(51)

The . . . the present invention may also contain other pharmaceutically active ingredients, for example, heparin, which has been shown to accelerate the **healing** of thermal burns. Other growth factors, such as TGF-.alpha., TGF-.beta., EGF, **FGF**, platelet factor 4, insulin or somatomedins (see Grotendorst et al., 1985) and angiogenesis factor, may also work synergistically with the PDGF analogs described herein. Antibiotics may also be included to keep the **wound** free of infection.

US PAT NO: 4,885,163 :IMAGE AVAILABLE: L6: 167 of 173
DATE ISSUED: Dec. 5, 1989
TITLE: Topical use of IGF-II for wound healing
INVENTOR: Carl J. Shaar, Indianapolis, IN
Michele C. Smith, Indianapolis, IN
ASSIGNEE: Eli Lilly and Company, Indianapolis, IN (U.S. corp.)
APPL-NO: 07/018,251
DATE FILED: Feb. 24, 1987
ART-UNIT: 111
PRIM-EXMR: Peter D. Rosenberg
LEGAL-REP: William C. Martens, Leroy Whitaker

US PAT NO: 4,885,163 :IMAGE AVAILABLE: L6: 167 of 173

SUMMARY:

BSUM(10)

Leitzel . . . (1983), investigated the effect of a number of topically applied mitogenic preparations, viz., dexamethasone and insulin, PDGF, fibroblast growth factor (**FGF**), thrombin, Defined medium F for Fibroblasts, liver cell supernatant, EGF, NGF, and colostrum, to **wounds** in Syrian hamsters. They conclude that none of these agents has any effect on accelerating the **healing** of skin **wounds**.

US PAT NO: 4,878,913 :IMAGE AVAILABLE: L6: 168 of 173
DATE ISSUED: Nov. 7, 1989
TITLE: Devices for neural signal transmission
INVENTOR: Patrick Aebischer, Providence, RI
Robert F. Valentini, Providence, RI
Pierre M. Galletti, Providence, RI
ASSIGNEE: Pfizer Hospital Products Group, Inc., New York, NY (U.S. corp.)
APPL-NO: 07/093,371
DATE FILED: Sep. 4, 1987
ART-UNIT: 332
PRIM-EXMR: Alan W. Cannon
LEGAL-REP: Thomas J. Engellenner, Ann L. Kerner

US PAT NO: 4,878,913 :IMAGE AVAILABLE: L6: 168 of 173

DETDESC:

DETD(16)

Activated . . . secreting growth or trophic factors into the regenerating environment. Growth factors may also be released by other

cells of the **wound healing** process, such as endothelial cells, e.g., endothelial derived growth factor (EDGF), and fibroblasts e.g., fibroblast growth factor (**FGF**).

US PAT NO: 4,876,242 :IMAGE AVAILABLE: L6: 169 of 173
DATE ISSUED: Oct. 24, 1989
TITLE: Human insulin-like growth factor analoges with reduced binding to serum carrier proteins and their production in yeast
INVENTOR: Joy D. Applebaum, North Brunswick, NJ
Marvin L. Bayne, Westfield, NJ
Margaret A. Cascieri, East Windsor, NJ
ASSIGNEE: Merck & Co., Inc., Rahway, NJ (U.S. corp.)
APPL-NO: 07/099,367
DATE FILED: Sep. 21, 1987
ART-UNIT: 186
PRIM-EXMR: Delbert R. Phillips
ASST-EXMR: Christina Chan
LEGAL-REP: David L. Rose, Hesna J. Pfeiffer

US PAT NO: 4,876,242 :IMAGE AVAILABLE: L6: 169 of 173

SUMMARY:

BSUM(65)

Because the hIGF-I analogs act synergistically with platelet-derived growth factor (PDGF) or other competence factors such as fibroblast growth factor (**FGF**) to stimulate DNA synthesis and cell replication in human fibroblasts, such analogs are useful to promote would **healing** especially in cases where endogenous hIGF levels are low. Thus, the instant IGF-I analogs may be administered in combination with PDGF or **FGF**. The compounds could be administered parenterally, either subcutaneously, intramuscularly or intravenously using pharmaceutically acceptable parenteral formulation ingredients such as those. . . preferably from 1 to 10 mg/kg. Preferably, however, the compounds are administered topically when used as an agent to promote **wound healing**. Typical formulations for topical application are liquid, paste, ointment and spray formulations. The formulations could also be incorporated into a dressing which would be applied to the **wound**. The dressing would slowly release the compound directly to the site needing treatment.

US PAT NO: 4,874,746 :IMAGE AVAILABLE: L6: 170 of 173
DATE ISSUED: Oct. 17, 1989
TITLE: Wound headling composition of TGF-alpha and PDGF
INVENTOR: Harry N. Antoniades, Newton, MA
Samuel E. Lynch, Jamaica Plain, MA
ASSIGNEE: Institute of Molecular Biology, Inc., Boston, MA (U.S. corp.)
President and Fellows of Harvard College, Cambridge, MA (U.S. corp.)
APPL-NO: 07/136,399
DATE FILED: Dec. 22, 1987
ART-UNIT: 186
PRIM-EXMR: Howard E. Schain
LEGAL-REP: Paul T. Clark

US PAT NO: 4,874,746 :IMAGE AVAILABLE: L6: 170 of 173

SUMMARY:

BSUM(4)

It has been proposed to use PDGF to promote in vivo **wound healing**. For example, Grotendorst (1984) J. Trauma 24: 549-52 describes adding PDGF to Hunt-Schilling wire mesh chambers impregnated with a collagen. . . . of new collagen synthesized. However, Leitzel et al. (1985) J. Dermatol. Surg. Oncol. 11: 617-22 were unable to accelerate normal **wound healing** in hamsters using PDGF alone or in combination with **FGF** and EGF.

US PAT NO: 4,861,757 :IMAGE AVAILABLE: L6: 171 of 173
DATE ISSUED: Aug. 29, 1989
TITLE: Wound healing and bone regeneration using PDGF and IGF-I
INVENTOR: Harry N. Antoniades, Newton, MA
Samuel E. Lynch, Jamaica Plain, MA
Ray C. Williams, Arlington, MA
ASSIGNEE: Institute of Molecular Biology, Boston, MA (U.S. corp.)
President and Fellows of Harvard College, Cambridge, MA (U.S. corp.)
APPL-NO: 07/120,943
DATE FILED: Nov. 16, 1987
ART-UNIT: 186
PRIM-EXMR: Howard E. Schain
LEGAL-REP: Paul T. Clark

US PAT NO: 4,861,757 :IMAGE AVAILABLE: L6: 171 of 173

SUMMARY:

BSUM(3)

It has been proposed to use PDGF to promote in vivo **wound healing**. For example, Grotendorst (1984) J. Trauma 24:549-52 describes adding PDGF to Hunt-Schilling wire mesh chambers impregnated with a collagen gel. . . . amount of new collagen synthesized. However, Leitzel et al. (1985) J. Dermatol. Surg. Oncol. 11:617-22 were unable to accelerate normal **wound healing** in hamsters using PDGF alone or in combination with **FGF** and EGF.

US PAT NO: 4,849,407 :IMAGE AVAILABLE: L6: 172 of 173
DATE ISSUED: Jul. 18, 1989
TITLE: Biologically active mosaic proteins
INVENTOR: Mark J. Murray, Seattle, WA
James D. Kelly, Seattle, WA
ASSIGNEE: ZymoGenetics, Inc., Seattle, WA (U.S. corp.)
APPL-NO: 06/941,970
DATE FILED: Dec. 15, 1986
ART-UNIT: 186
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Seed and Berry

US PAT NO: 4,849,407 :IMAGE AVAILABLE: L6: 172 of 173

DETDESC:

DETD(58)

The . . . the present invention may also contain other pharmaceutically active ingredients, for example, heparin, which has been shown to accelerate the **healing** of thermal burns. Other growth factors, such as TGF-.alpha., TGF-.beta., EGF, **FGF**, platelet factor 4, insulin or somatomedins (see Grotendorst et al., 1985) and angiogenesis factor, may also work synergistically with the PDGF analogs described herein. Antibiotics may also be included to keep the **wound**

free of infection.

US PAT NO: 4,845,075 :IMAGE AVAILABLE: L6: 173 of 173
DATE ISSUED: Jul. 4, 1989
TITLE: Biologically active B-chain homodimers
INVENTOR: Mark J. Murray, Seattle, WA
James D. Kelly, Seattle, WA
ASSIGNEE: ZymoGenetics, Inc., Seattle, WA (U.S. corp.)
APPL-NO: 06/942,161
DATE FILED: Dec. 15, 1986
ART-UNIT: 186
PRIM-EXMR: Delbert R. Phillips
LEGAL-REP: Seed and Berry

US PAT NO: 4,845,075 :IMAGE AVAILABLE: L6: 173 of 173

DETDESC:

DETD(52)

The . . . the present invention may also contain other pharmaceutically active ingredients, for example, heparin, which has been shown to accelerate the **healing** of thermal burns. Other growth factors, such as TGF-.alpha., TGF-.beta., EGF, **FGF**, platelet factor 4, insulin or somatomedins (see Knighton et al., ibid.; Lawrence et al., ibid.; Sporn et al., Science 219:. . . an angiogenesis factor, may also work synergistically with the proteins described herein. Antibiotics may also be included to keep the **wound** free of infection.